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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/750,076	12/31/2003	Sidney N. Wolfe	PP16022.017 (35784/271881	2260

45853 7590 10/05/2006

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INTELLECTUAL PROPERTY - R440
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EXAMINER	
HISSONG, BRUCE D	

ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 10/05/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/750,076	WOLFE ET AL.	
	Examiner	Art Unit	
	Bruce D. Hissong, Ph.D.	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 February 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-35* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2/5/2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *sequence comparison 1*.

DETAILED ACTION

Formal Matters

1. Applicants' preliminary amendment to the specification was received on 2/5/2004, and has been entered into the record.

2. Claims 1-35 are pending and are the subject of this office action.

Information Disclosure Statement

The information disclosure statement received on 2/5/2004 has been fully considered by the Examiner.

Claim Objections

Claims 5, 6, 13, 14, 19, 20, 27, 28, 33, and 34 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. In the instant case, independent claims 1, 8, 16, 22, and 30 recite methods for preparing an injectable formulation of IFN-β, while dependent claims 5, 13, 19, 27, and 33 recite IFN-β that is glycosylated or unglycosylated, and dependent claims 6, 14, 20, 28, and 34 recite IFN-β that is recombinantly produced. Claims 5, 6, 13, 14, 19, 20, 27, 28, 33, and 34 do not further limit the subject matter of claims 1, 8, 16, 22, and 30 because these claims are drawn to methods of preparing an injectable formulation of IFN-β. The glycosylated or unglycosylated or recombinant IFN-β recited in claims 5, 6, 13, 14, 19, 20, 27, 28, 33, and 34 would perform the same role or function as the IFN-β of claims 1, 8, 16, 22, and 30, and additionally, would have the same sequence and structure, unless Applicants can provide evidence to the contrary.

Claim Rejections - 35 USC § 112, first paragraph - enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-35 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods for preparing an injectable formulation of interferon (IFN)-β, wherein the IFN-β is full-length IFN-β or the polypeptide of SEQ ID NO: 1 or 2, does not reasonably provide enablement for methods for preparing an injectable formulation of IFN-β wherein the IFN-β is a variant, fragment, or other derivative of full-length IFN-β. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The factors to be considered when determining if the disclosure satisfies the enablement requirement have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, and the breath of claims. Ex Parte Forman, (230 USPQ 546 (Bd. Pat. App. & Int. 1986); In re Wands, 858 F.2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988).

The instant specification, on pages 6-10, define the terms "IFN-β" or "IFN-beta" as native, mature IFN-β, the polypeptides defined by SEQ ID NOs 1 or 2, or other variants, fragments, or truncated forms of IFN-β. In light of these teachings, the claims are drawn to not only the polypeptides of SEQ ID NOs 1 or 2, but also any variant, fragment, or truncated form of IFN-β. The claims are further drawn to IFN-β polypeptides with at least 80% homology to the polypeptide of SEQ ID NO: 1, and therefore, the claims are drawn to methods of preparing an injectable formulation of IFN-β, wherein said IFN-β comprises an unreasonable number of polypeptides. Although the specification is enabling for mature, native IFN-β (SEQ ID NO: 1) or the polypeptide of SEQ ID NO: 2, there is no guidance or examples showing any other variant, fragment, or truncated IFN-β, or any polypeptide with less than 100% sequence identity to SEQ ID NO: 1, that could be prepared by the claimed methods and still retain any biological function which would provide utility to the injectable formulation. The specification does not teach which amino acids residues, or regions/domains of the protein, can be altered and still produce an

IFN-β polypeptide that can be formulated by the claimed methods and still retain biological function.

It is known in the art that even single amino acid changes or differences in the amino acid sequence of a protein can have dramatic effects on the protein's function. As an example of the unpredictable effects of mutations on protein function, Mickel *et al* (Med. Clin. North Am., 2000, Vol. 84(3), p. 597-607) teaches that cystic fibrosis is an autosomal recessive disorder caused by abnormal function of a chloride channel, referred to as the cystic fibrosis transmembrane conductance regulator (CFTR – p. 597). Several mutations can cause cystic fibrosis, including the G551D mutation. In this mutation, a glycine replaces the aspartic acid at position 551, giving rise to the cystic fibrosis phenotype. In the most common cystic fibrosis mutation, Δ-F508, a single phenylalanine is deleted at position 508, giving rise to the cystic fibrosis phenotype. Thus, even the substitution or deletion of a single amino acid can have dramatic and *unpredictable* effects on the function of the protein. Due to this uncertainty, a person of ordinary skill in the art would not be able to predict which amino acid residues, or polypeptide regions/domains, could be altered and still retain biological activity. Such a determination would require further, undue experimentation on the part of the skilled artisan.

In summary, due to the excessive breadth of the claims, which read on methods of preparing an injectable formulation of IFN-β, wherein said IFN-β can be any variant, derivative, or polypeptide with at least 80% homology to SEQ ID NO: 1, the lack of guidance and examples in the specification that teach which amino acid residues or polypeptide domains/regions can be altered, and the unpredictability inherent in the art regarding such alterations, a person or ordinary skill in the art would require further, undue experimentation to practice the methods of the instant application commensurate in scope with the claims.

Claim Rejections - 35 USC § 112, first paragraph – written description

Claims 1-35 are rejected under 35 U.S.C. 112, first paragraph, containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to methods of preparing an injectable formulation of IFN-β. The claims do not require the IFN-β polypeptides of the instant invention to have any biological

activity, nor any particular structure. As stated in the previous enablement rejection, the claims read on mature, native IFN-β, as well as any variant, fragment, truncated IFN-β polypeptide, or any polypeptide that is at least 80% identical to SEQ ID NO: 1. Although the specification does describe some examples of IFN-β polypeptides that can be used in the claimed method, these examples are insufficient to define the genus of IFN-β polypeptides, which can encompass any variant, fragment, or truncated IFN-β polypeptide. Thus, the claims are drawn to a genus of polypeptides that has not been adequately described in the specification.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the only factor present in the claims is a requirement that the IFN-β polypeptides be variants, fragments, or other modified IFN-β polypeptides. There is no identification of any particular portion of mature, native IFN-β that must be conserved in order to maintain function. Accordingly, in the absence of sufficient distinguishing characteristics, the specification does not provide adequate written description of the claimed genus.

Claim Rejections - 35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 7, 15, 21, 29, and 35 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims are drawn IFN-β polypeptides having at least 80% amino acid sequence identity to SEQ ID NO: 1, as calculated using the ALIGN program. However, it is not clear which version/year of the ALIGN program must be used, and therefore the claim is indefinite.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

1. Claims 8-35 are rejected under 35 U.S.C. 103(a) as being unpatentable over in view of Arora *et al* (*J. Biotech.* 1996, Vol. 52, p. 127-133), in view of Dorin *et al* (US 5,814,485). The claims of the instant invention are drawn to methods of preparing an injectable formulation of IFN-β, wherein said methods comprise denaturing IFN-β by dissolving said IFN-β in guanidine hydrochloride followed by renaturation of IFN-β by dilution into a buffer. In some cases, the claims are also drawn to methods comprising removal of guanidine by diafiltration or dialysis into a second buffer. The claims also recite buffers of various pH and guanidine concentrations, and IFN-β that is glycosylated or unglycosylated, produced recombinantly, or represented by the amino acid sequences set forth in SEQ ID NOs 1 or 2.

Arora *et al* teaches methods of preparing properly folded recombinant IFN-γ. Specifically, Arora *et al* discloses a method whereby IFN-γ present in E. coli inclusion bodies is dissolved in guanidine hydrochloride, followed by renaturation of the dissolved IFN-γ by dilution in refolding buffer at pH 8.0, with or without arginine. The renatured IFN-γ was then dialyzed against a second buffer at pH 8.0 (see p. 130, paragraphs 3.5-3.7). Arora *et al* is silent regarding guanidine hydrochloride concentrations after dilution or dialysis, a first buffer with a pH between 3.0 and 5.0, or purification of any IFN-β polypeptide.

Dorin *et al* discloses a polypeptide sequence (SEQ ID NO: 1 of Dorin *et al*) with 100% identity to SEQ ID NO: 1 of the instant application (see sequence comparison 1), and teaches that IFN-β is useful for treatment of diseases such as multiple sclerosis and hepatitis b or c (column 1, lines 14-20).

A person of ordinary skill in the art would have been motivated, at the time the instant invention was conceived, to combine the teachings of Arora *et al* and Dorin *et al* to practice a method that is commensurate in scope with the claims of the instant invention. The motivation to do so comes from the teaching of Arora *et al*, which shows that IFN polypeptides can be purified and properly folded by first dissolving the polypeptides in guanidine, followed by dilution

into a buffer to renature the IFN polypeptides, and finally, dialysis to remove the guanidine. Further motivation comes from the teachings of Dorin *et al*, which teaches an IFN-β polypeptide with 100% sequence identity to SEQ ID NO: 1 of the instant application, and the usefulness of this polypeptide in the treatment of human disease. In addition, Dorin *et al* discloses production of this IFN-β polypeptide in E. coli, and thus the IFN-β polypeptide taught by Dorin *et al* would be a recombinant IFN-β polypeptide that is unglycosylated. The combined teachings of Arora *et al* and Dorin *et al* would provide a skilled artisan with knowledge of a method of purification which produces properly folded IFN polypeptides, and an IFN-β polypeptide which is useful for administration to humans for treatment of disease. Thus, a person of ordinary skill in the art would be motivated to purify the IFN-β polypeptide of Dorin *et al*, or any other IFN-β polypeptide, by the method taught by Arora *et al*. Although the method of Arora et al does not specifically teach the claimed pH ranges of the first buffer or the claimed guanidine concentrations, the skilled artisan would have the motivation and the ability to optimize the experimental conditions. Therefore, claims 8-35 of the instant application are obvious in view of the combined teachings of Arora *et al* and Dorin *et al*.

2. Claims 1-7 are rejected under 35 U.S.C. 103(a) as being unpatentable over van Oss (*J. Protein Chem*. 1989, Vol. 5, p. 661-668 – cited in the information disclosure statement received on 2/5/2004), in view of Arora *et al*, and further in view of Dorin *et al*. The subject matter of the claims is discussed *supra*. Claims 1-7 are further drawn to a method of preparing an injectable formulation of IFN-b, wherein said method comprises a first step of precipitating IFN-β using an alcohol, followed by purification as described in the preceding rejection.

The disclosures of Arora *et al* and Dorin *et al* are described *supra*, and both references are silent regarding precipitation of IFN-β using an alcohol. van Oss teaches that ethanol precipitation of proteins is well-known in the art and is a common and accepted method of protein isolation (p 661, 1st paragraph).

It would have been obvious to a person of ordinary skill in the art, at the time the instant invention was conceived, to combine the teachings of van Oss, Arora *et al*, and Dorin *et al* to practice a method of preparing an injectable formulation of IFN-β that is commensurate in scope with the claims of the instant invention. By teaching that ethanol precipitation of proteins is a common and effective procedure for protein isolation, van Oss provides the motivation to incorporate ethanol precipitation of IFN-β into the method taught by the combination of Arora *et*

al and Dorin *et al*, as described in the preceding rejection. Thus, the combined teachings of van Oss, Arora *et al*, and Dorin *et al* provide the motivation to practice a method that is commensurate in scope with claims 1-7 of the instant application, and therefore claims 1-7 are obvious in view of the combined teachings of van Oss, Arora *et al*, and Dorin *et al*.

Conclusion

No claim is allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bruce D. Hissong, Ph.D., whose telephone number is (571) 272-3324. The examiner can normally be reached M-F from 8:30am - 5:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Nickol, Ph.D., can be reached at (571) 272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

BDH
Art Unit 1646

GARY B. NICKOL, PH.D.
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

SEQUENCE COMPARISON 1

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RESULT 1
US-08-477-310A-1
; Sequence 1, Application US/08477310A
; Patent No. 5814485
;  GENERAL INFORMATION:
;    APPLICANT:  Dorin, Glenn
;    APPLICANT:  McAlary, Patrick J.
;    APPLICANT:  Wong, Kathleen M.
;    TITLE OF INVENTION:  Bacterial Production of Hydrophobic
;    TITLE OF INVENTION:  Polypeptides
;    NUMBER OF SEQUENCES:  3
;    CORRESPONDENCE ADDRESS:
;      ADDRESSEE:  Chiron Corporation
;      STREET:  4560 Horton Street
;      CITY:  Emeryville
;      STATE:  California
;      COUNTRY:  U.S.A.
;      ZIP:  94608
;    COMPUTER READABLE FORM:
;      MEDIUM TYPE:  Floppy disk
;      COMPUTER:  IBM PC compatible
;      OPERATING SYSTEM:  PC-DOS/MS-DOS
;      SOFTWARE:  PatentIn Release #1.0, Version #1.30
;    CURRENT APPLICATION DATA:
;      APPLICATION NUMBER:  US/08/477,310A
;      FILING DATE:  06-JUN-1995
;      CLASSIFICATION:  435
;    ATTORNEY/AGENT INFORMATION:
;      NAME:  Chung, Ling-Fong
;      REGISTRATION NUMBER:  36,482
;      REFERENCE/DOCKET NUMBER:  960.001
;    TELECOMMUNICATION INFORMATION:
;      TELEPHONE:  (510) 923-2704
;      TELEFAX:  (510) 655-3542
;  INFORMATION FOR SEQ ID NO:  1:
;    SEQUENCE CHARACTERISTICS:
;      LENGTH:  166 amino acids
;      TYPE:  amino acid
;      STRANDEDNESS:  single
;      TOPOLOGY:  linear
;    MOLECULE TYPE:  protein
US-08-477-310A-1

  Query Match             100.0%;  Score 874;  DB 1;  Length 166;
  Best Local Similarity   100.0%;  Pred. No. 1.7e-84;
  Matches  166;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps    0;

Qy          1 MSYNLLGFLQRSSNFQCQKLLWQLNGRLEYCLKDRMNFDIPEEIKQLQQFQKEDAALTIY 60
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db          1 MSYNLLGFLQRSSNFQCQKLLWQLNGRLEYCLKDRMNFDIPEEIKQLQQFQKEDAALTIY 60

Qy         61 EMLQNIFALFRQDSSSTGWNETIVENLLANVYHQINHLKTVLEEKLEKEDFTRGKLMSSL 120
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         61 EMLQNIFALFRQDSSSTGWNETIVENLLANVYHQINHLKTVLEEKLEKEDFTRGKLMSSL 120

Qy        121 HLKRYYGRILHYLKAKEYSHCAWTIVRVEILRNFYFINRLTGYLRN 166
              ||||||||||||||||||||||||||||||||||||||||||||||
Db        121 HLKRYYGRILHYLKAKEYSHCAWTIVRVEILRNFYFINRLTGYLRN 166
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